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⑤④ **Novel 9 alpha-fluoro- or chloro-corticosteroid esters and a process for their preparation.**

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GB-A- 963 717
GB-A-1 047 519
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The file contains technical information
submitted after the application was filed and
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Courier Press, Leamington Spa, England.

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**CHEMICAL ABSTRACTS, vol. 87, n. 3, 18th July
1977, page 688, no. 23618t, Columbus, Ohio,
US; & JP - A - 76 149 258 (TAKEDA CHEMICAL
INDUSTRIES LTD.) 22-12-1976**

**CHEMICAL ABSTRACTS, vol. 88, no. 23, 5th
June 1978, page 619, no. 170388s, Columbus,
Ohio, US; & JP - A - 77 144 663 (TAISHO
PHARMACEUTICAL CO., LTD.) 02-12-1977**

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D scription

Corticosteroids have been long known for their anti-inflammatory activity. It has been similarly known that the anti-inflammatory activity can be considerably enhanced by the introduction of ester functions at the 17- and 21-positions. The present invention concerns certain novel 17,21-diacylates of corticosteroids and their preparation.

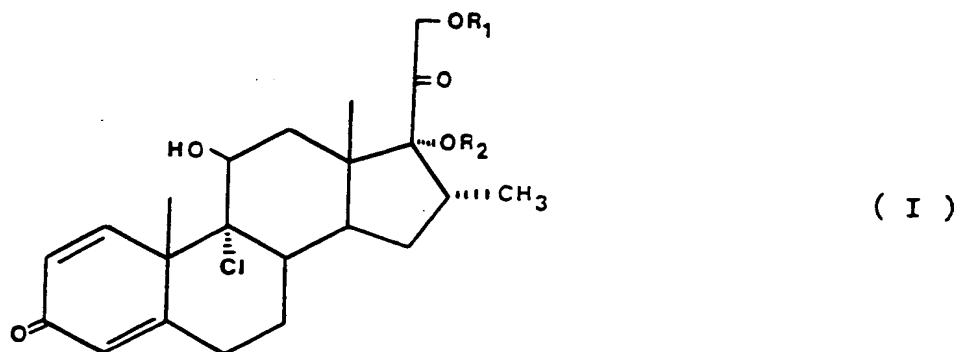
The preparation of such esterified corticosteroids according to the prior art can be split into three major groups.

The first is by esterification without protection at the 11-position. This is exemplified in British Patent 737,291. This process suffers from a lack of specificity for the required 17,21-diacylated product, when the 11-substituent is a hydroxyl group.

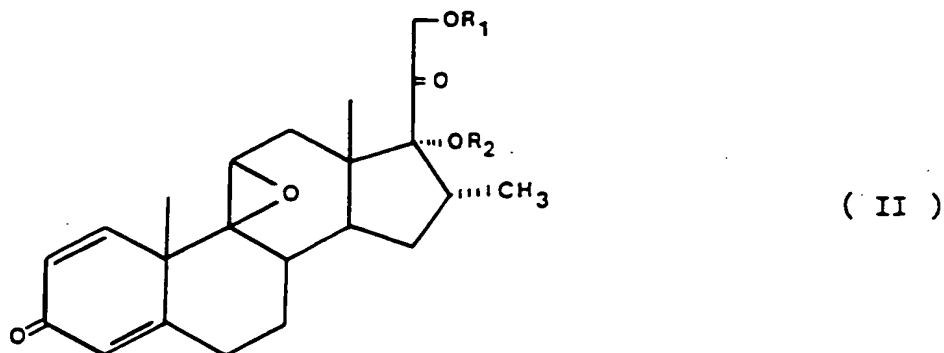
The second general method is the use of 11-hydroxyl protection, prior to esterification. Protection by a trihaloacetyl group, the trimethylsilyl ether group, the tetrahydropyran-2'-yl group, and the nitrate ester have all been proposed, variously in British Patents 1,097,165, 1,227,992 and 1,082,573 and US Patent 4,024,131. The following esterification can be accomplished by a wide variety of methods, with the best being described in European Patent Specification 72,200. All of these processes are somewhat lengthy due to the necessity of introducing and then removing the 11-protecting group.

The final general method is by the acid hydrolysis of 17,21-orthoesters, which can be prepared without 11-protection, followed by 21-acylation. However, the necessary trialkyl orthoester reagents are difficult to prepare and usually not commercially available, added to the fact that the acid hydrolysis often gives mixtures of the 17-monoester and 21-monoester, plus variable amounts of the 17,21-dihydroxy starting material. This method is described in British Patents 996,079, 996,080, 1,043,347, 1,047,518 and 1,047,519, as well as abstract in Chem. Abs. 87, 23618t, (1977) reporting on JP-A-76/149,259.

According to the present invention there is provided 17,21-diacylates of 9 α -chloro-17,21-dihydroxy-corticosteroids of the formula



wherein R₁ and R₂ each represent an acyl group of 2 to 6 carbon atoms or a benzoyl group and where R₁ and R₂ can be the same or different in the same molecule, with the exclusion from the above of the compounds where R₁ and R₂ are propionyl; R₁ is acetyl and R₂ is propionyl; and R₁ is acetyl and R₂ is valeryl. These compounds are prepared from a compound of the formula



wherein R₁ and R₂ have the significance given above, which is reacted with hydrogen chloride.

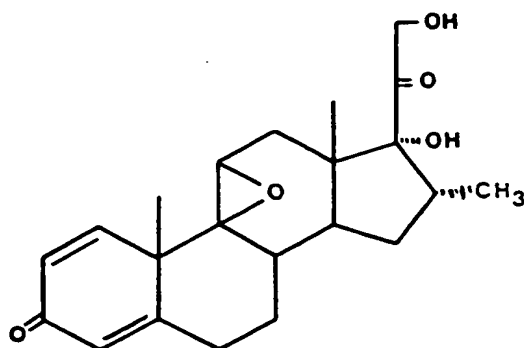
Whilst the process of chlorination of a 9,11-epoxide per se is known in the literature, for example in US Patent 4,154,748, in British Patent 1,296,458 and in European Patent Application 29,151, we have now

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discovered that the process can be applied to a starting material of formula II, allowing the preparation of steroidal esters which have significant anti-inflammatory activity when compared with other known corticosteroid esters.

French Patent 2,306,214 and the abstract in Chem. Abs. 88, 170388s, (1978) reporting on JP—A—77/144,663 describe a process to prepare 21-halo-steroid 17-monoesters, by reacting the corresponding 17,21-orthoester with a halogenating agent. Such compounds are said to be useful as anti-inflammatory agents, although no quantification of typical examples is given.

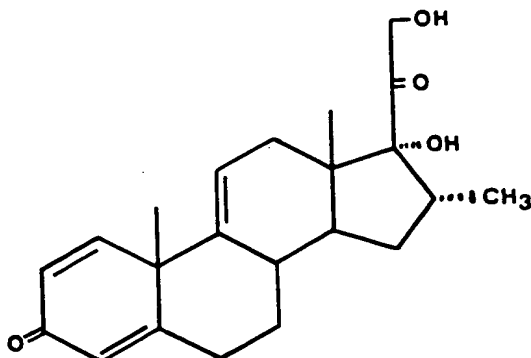
The starting materials can be prepared according to the known processes, such as diesterification of



(III)

when symmetrical diesters are required. When non-symmetrical 17,21-diester are required, the 21-acrylate of the compound of formula III is used as starting material. Alternatively, the 17,21-orthoester can be prepared, followed by acid hydrolysis to give the 17-monoester, which is then acylated at the 21-position. By this method, both symmetrical and non-symmetrical 17,21-diester are available.

Alternatively, the compound



(IV)

is diacylated by either of the methods given above, then reacted with a reagent capable of producing hypobromous acid in situ (such as N-bromoacetamide in the presence of perchloric acid) to give the 9 α -bromo-11 β -hydroxyl compound, followed by epoxidation, for example using potassium acetate.

The starting material is dissolved in an organic solvent, or a mixture of such. The solvents useful in the present invention comprise dimethylformamide, tetrahydrofuran, dioxan, ketones such as acetone, halogenated hydrocarbons such as chloroform, and lower alcohols with 1 to 3 carbon atoms. The solution is then cooled to between -60°C and 0°C , preferably between -30°C and -5°C .

The hydrogen chloride is dissolved in an organic solvent, which can be the same or different from that used in the dissolution of the steroidal starting material, or in water. The concentration is preferably between about 35% and about 75% weight/weight.

After cooling, the acid solution is added slowly to the steroid solution ensuring that the temperature does not rise above the selected reaction temperature. After the addition, the reaction mixture is stirred at a controlled temperature of between -60°C and $+20^{\circ}\text{C}$, preferably between -20°C and $+10^{\circ}\text{C}$.

After completion of the reaction, the reaction mixture is treated with a cold non-solvent, which is miscible with the reaction mixture and in which the required product is insoluble. A preferred non-solvent is a mixture of water and ice. Additionally, the non-solvent can be mixed with a base prior to addition to the reaction mixture. The group of useful bases comprises sodium carbonate, sodium bicarbonate, ammonia solution and an organic amine, such as triethylamine. The quantity of base is calculated such that the pH of the mixture after precipitation is between 3 and 7. Above pH 7, there would be present free base which could cause hydrolysis or solvolysis of the 17- and/or 21-ester functions.

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Alternatively, the base can be added after the precipitation of the required product.

In either case the temperature of the precipitation should be controlled, so as not to allow rise significantly during the neutralisation of the acid reagent. Preferably it should be kept below or about 0°C during the actual precipitation. The product can then be recovered by conventional means, such as filtration, followed by drying.

Thus, the compounds of formula I can be prepared in good yield and purity, with the advantage of not causing hydrolysis of the ester functions.

The novel compounds of the present invention were shown to have surprising anti-inflammatory activity. Thus, in the rat's food oedema test it was shown that most of the compounds were as good as or better than the standard of betamethasone 17-valerate. More concretely, the 17-propionate 21-butyrate and the 17,21-dibutyrate of 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione were several times more active than the standard. Similarly, in the vasoconstriction test described originally by A. W. McKenzie and R. B. Stoughton in Arch. Derm. 86, 608—610 (1962), several of the novel compounds were shown to be more active than the betamethasone 17-valerate standard, especially the aforementioned 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 17-propionate 21-butyrate.

The compounds are novel per se and include the following 17,21-diacylates of 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione:—

- 17,21-diacetate
- 17-acetate 21-propionate
- 17-acetate 21-butyrate
- 17-acetate 21-valerate
- 17-acetate 21-benzoate
- 17-propionate 21-butyrate
- 17-propionate 21-valerate
- 17-butyrate 21-acetate
- 17-butyrate 21-propionate
- 17,21-butyrate
- 17-butyrate 21-valerate
- 17-butyrate 21-benzoate
- 17-valerate 21-propionate
- 17-valerate 21-butyrate

The products of the present invention when mixed with pharmaceutically acceptable excipients and diluents, well known to those skilled in the art, are active in locally applied topical formulations. Thus, the present invention includes pharmaceutical compositions which comprise a novel compound of the invention, and an inert pharmaceutically acceptable carrier therefor.

Typical of the formulations are creams, lotions, ointments, eye-drops and oral inhalation sprays. The content of the active principle depends on the actual formulation, but is generally between 0.001% w/w and 0.5% w/w, more preferably between 0.01% and 0.25% w/w.

The formulations prepared with the products of the present invention can be used in the topical treatment of corticosteroid-responsive dermatoses, which may include psoriasis, eczemas, neurodermatitis, seborrheic dermatitis, contact dermatitis, atopic dermatitis and intertrigo.

The following examples serve to illustrate the present invention, without in any way limiting the scope thereof.

All U.V. values quoted are in terms of $E_{1\%}^{1\text{cm}}$.

Example 1

Preparation of 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 17-propionate 21-benzoate

9 β ,11 β -Epoxy-17 α ,21-dihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 17-propionate 21-benzoate (400 mg; 0.785 mmoles) was added slowly with stirring to a pre-cooled solution of hydrogen chloride in dimethylformamide (50%; 4 ml) maintained at -5°C. The reaction mixture was stirred for 2 hours and 30 minutes at a temperature of -5°C to 0°C, and then precipitated in ice/water (40 ml) containing ammonia solution (25%; 3 ml). The resulting mixture was then neutralised, the solid filtered, washed with water and dried at 35°C. The yield was 410 mg (96% of theoretical).

m.p. = 245—6°C

$\{\alpha\}_D^{25} = +61.5^\circ$ (dioxan)

U.V. = 468 at 234 nm (methanol)

Example 2

The following 17,21-diacylates of 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione were prepared using the method of Example 1:—

17,21-diacetate

m.p. = 240—2°C

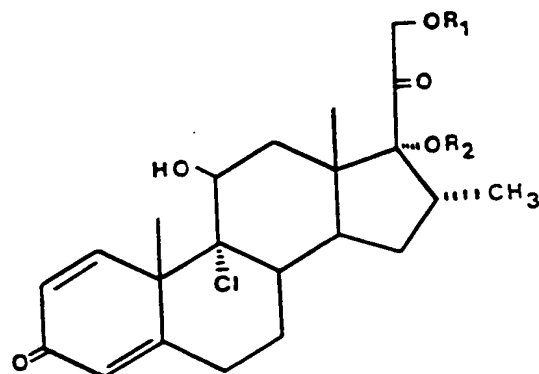
$\{\alpha\}_D^{25} = +55.8^\circ$ (dioxan)

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- U.V. = 312 at 240 nm (methanol)
- 17-acetate 21-propionate
m.p. = 222—3°C
{ α }_D²⁵ = +55.5° (dioxan)
- 5 U.V. = 303 at 239—240 nm (methanol)
- 17-acetate 21-butyrate
m.p. = 200—1°C
{ α }_D²⁵ = +53.6° (dioxan)
U.V. = 298 at 240 nm (methanol)
- 10 17-acetate 21-valerate
m.p. = 215—6°C
{ α }_D²⁵ = +53.9° (dioxan)
U.V. = 291 at 239—240 nm (methanol)
- 17-acetate 21-benzoate
15 m.p. = 243—4°C (decomp.)
{ α }_D²⁵ = +61.7° (dioxan)
U.V. = 483 at 233 nm (methanol)
- 17-propionate 21-butyrate
m.p. = 231—2°C
20 { α }_D²⁵ = +54.2° (dioxan)
U.V. = 288 at 240 nm (methanol)
- 17-propionate 21-valerate
m.p. = 227—8°C
{ α }_D²⁵ = +55.0° (dioxan)
25 U.V. = 280 at 238—9 nm (methanol)
- 17-propionate 21-benzoate
m.p. = 245—6°C (decomp.)
{ α }_D²⁵ = +61.5° (dioxan)
U.V. = 468 at 234 nm (methanol)
- 30 17-butyrate 21-acetate
m.p. = 212—3°C
{ α }_D²⁵ = +52.5° (dioxan)
U.V. = 294 at 239—240 nm (methanol)
- 17-butyrate 21-propionate
35 m.p. = 220—1°C
{ α }_D²⁵ = +55.5° (dioxan)
U.V. = 287 at 239—240 nm (methanol)
- 17,21-dibutyrate
m.p. = 219—220°C
40 { α }_D²⁵ = +53.3° (dioxan)
U.V. = 281 at 239—240 nm (methanol)
- 17-butyrate 21-valerate
m.p. = 193—4°C
{ α }_D²⁵ = +54.4° (dioxan)
45 U.V. = 274 at 238—9 nm (methanol)
- 17-butyrate 21-benzoate
m.p. = 219—220°C
{ α }_D²⁵ = +59.0° (dioxan)
U.V. = 456 at 233—4 nm (methanol)
- 50 17-valerate 21-propionate
m.p. = 181—2°C
{ α }_D²⁵ = +54.3° (dioxan)
U.V. = 282 at 239 nm (methanol)
- 17-valerate 21-butyrate
55 m.p. = 199—200°C
{ α }_D²⁵ = +51.4° (dioxan)
U.V. = 275 at 240 nm (methanol)
- 17,21-divalerate
m.p. = 165—6°C
60 { α }_D²⁵ = +52.2° (dioxan)
U.V. = 266 at 239—240 nm (methanol)
- 17-valerate 21-benzoate
m.p. = 187—190°C
{ α }_D²⁵ = +55.7° (dioxan)
65 U.V. = 445 at 233 nm (methanol)

Claims

1. A compound of the formula



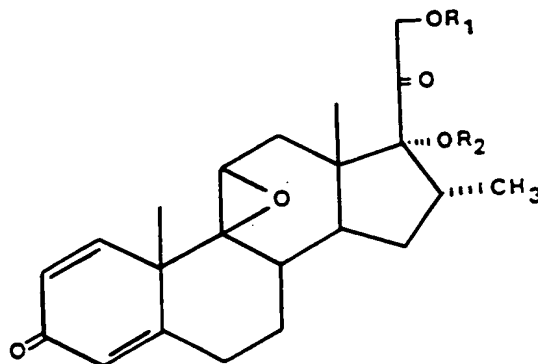
(I)

wherein R_1 and R_2 each represent an acyl group of 2 to 6 carbon atoms or a benzoyl group and where R_1 and R_2 can be the same or different in the same molecule, with the exclusion from the above of the compounds where R_1 is propionyl and R_2 is propionyl; R_1 is acetyl and R_2 is propionyl; and R_1 is acetyl and R_2 is valeryl.

2. The compounds:

9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 17,21-diacetate
 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 17-acetate 21-propionate
 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 17-acetate 21-butyrate
 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 17-acetate 21-valerate
 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 17-propionate 21-butyrate
 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 17-propionate 21-valerate
 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 17-butyrate 21-acetate
 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 17-butyrate 21-propionate
 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 17,21-dibutyrate
 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 17-butyrate 21-valerate
 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 17-butyrate 21-benzoate
 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 17-valerate 21-propionate
 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione 17-valerate 21-butyrate

3. A process for the preparation of the compounds of claim 1, characterised by the fact that a compound of the formula



(II)

wherein R_1 and R_2 are as defined in claim 1, is reacted with hydrogen chloride.

4. A process according to claim 3, characterised by the fact that excess hydrogen chloride is mixed with an organic solvent or with water, and the reaction temperature is controlled between -60°C and $+20^{\circ}\text{C}$.

5. A process according to claim 4, characterised by the fact that the reaction temperature is controlled between -20°C and $+10^{\circ}\text{C}$.

6. A process according to claims 3 and 4, characterised by the fact that the final product of the reaction is isolated by mixture with a non-solvent at a temperature about 0°C and the final pH of the reaction mixture is between 3 and 7.

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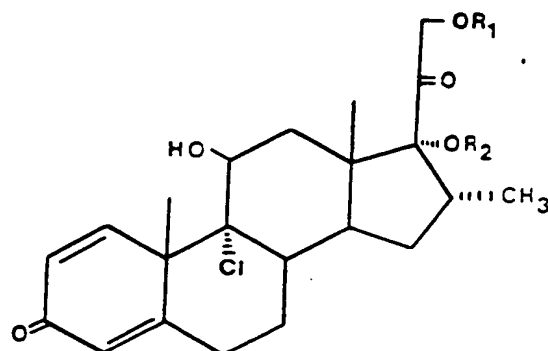
7. A process according to claim 6, characterised by the fact that the non-solvent is water and ice, and the pH is adjusted with sodium carbonate or bicarbonate, ammonia solution or an organic amine.

8. A pharmaceutical composition which contains a compound of formula I, as defined in claim 1, together with a pharmaceutical carrier.

9. A pharmaceutical composition according to claim 8, which contains any one of the compounds claimed in claim 2.

Patentansprüche

1. Verbindung der Formel



(I)

in der

R¹ und R² jeweils eine Acyl-Gruppe mit 2 bis 6 Kohlenstoff-Atomen oder eine Benzoyl-Gruppe darstellen und worin R₁ und R₂ in demselben Molekül gleich oder verschieden sein können, wobei von den vorgenannten Verbindungen diejenigen, worin

R₁ und R₂ Propionyl sind,

R₁ Acetyl ist und R₂ Propionyl ist und

R₁ Acetyl ist und R₂ Valeryl ist,

ausgeschlossen sind.

2. Die Verbindungen

9α-Chloro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-dien-3,20-dion-17,21-diacetat,

9α-Chloro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-dien-3,20-dion-17-acetat-21-propionat,

9α-Chloro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-dien-3,20-dion-17-acetat-21-butytrat,

9α-Chloro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-dien-3,20-dion-17-acetat-21-valerat,

9α-Chloro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-dien-3,20-dion-17-acetat-21-benzoat,

9α-Chloro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-dien-3,20-dion-17-propionat-21-butytrat,

9α-Chloro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-dien-3,20-dion-17-propionat-21-valerat,

9α-Chloro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-dien-3,20-dion-17-butytrat-21-acetat,

9α-Chloro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-dien-3,20-dion-17-butytrat-21-propionat,

9α-Chloro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-dien-3,20-dion-17-butytrat-21-dibutytrat,

9α-Chloro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-dien-3,20-dion-17-butytrat-21-valerat,

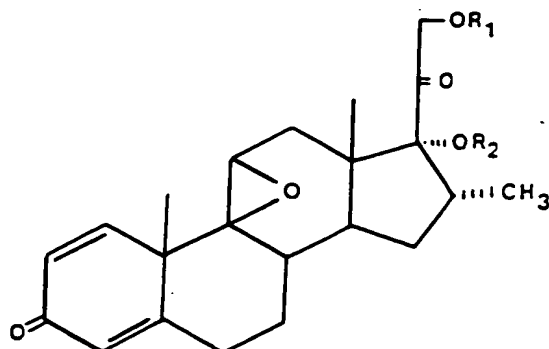
9α-Chloro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-dien-3,20-dion-17-butytrat-21-benzoat,

9α-Chloro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-dien-3,20-dion-17-valerat-21-propionat,

9α-Chloro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-dien-3,20-dion-17-valerat-21-butytrat.

3. Verfahren zur Herstellung der Verbindungen nach Anspruch 1, dadurch gekennzeichnet, daß eine

Verbindung der Formel



(II)

in der R₁ und R₂ die in Anspruch 1 angegebenen Bedeutungen haben, mit Hydrogenchlorid umgesetzt wird.

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4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß überschüssiges Hydrogenchlorid mit einem organischen Lösungsmittel oder mit Wasser vermischt wird und die Reaktionstemperatur zwischen -60°C und $+20^{\circ}\text{C}$ gesteuert wird.

5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß die Reaktionstemperatur zwischen -20°C und $+10^{\circ}\text{C}$ gesteuert wird.

6. Verfahren nach den Ansprüchen 3 und 4, dadurch gekennzeichnet, daß das Endprodukt der Reaktion durch Vermischung mit einem Nicht-Lösungsmittel bei einer Temperatur von etwa 0°C isoliert wird und der abschließende pH-Wert der Reaktionsmischung zwischen 3 und 7 liegt.

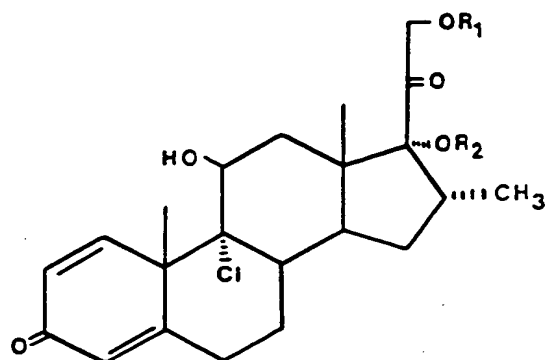
7. Verfahren nach Anspruch 6, dadurch gekennzeichnet, daß das Nicht-Lösungsmittel Wasser und Eis ist und der pH-Wert mit Natriumcarbonat oder -bicarbonat, Ammoniak-Lösung oder einem organischen Amin eingestellt wird.

8. Pharmazeutische Zusammensetzung, enthaltend eine Verbindung der Formel I, wie sie in Anspruch 1 definiert ist, zusammen mit einem pharmazeutischen Träger.

9. Pharmazeutische Zusammensetzung nach Anspruch 8, enthaltend irgendeine der Verbindungen nach Anspruch 2.

Revendications

1. Composé de la formule:



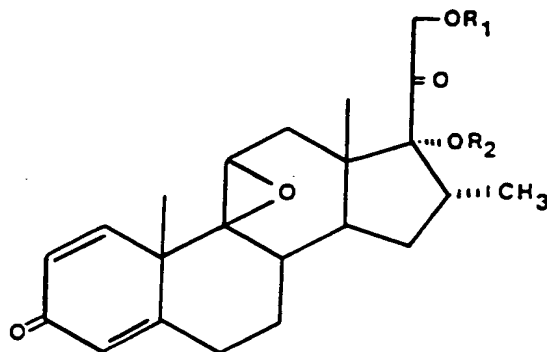
dans laquelle R_1 et R_2 représentent chacun un groupe acyle de 2 à 6 atomes de carbone ou un groupe benzoyle et où R_1 et R_2 peuvent être identiques ou différents dans la même molécule, à l'exclusion de ce qui précède des composés où R_1 et R_2 sont du propionyle, R_1 est de l'acétyl et R_2 est du propionyle, et R_1 est de l'acétyl et R_2 est du valéryle.

2. Les composés:

17,21-diacétate de 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -méthylprégna-1,4-diène-3,20-dione
 17-acétate 21-propionate de 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -méthylprégna-1,4-diène-3,20-dione
 17-acétate 21-butyrate de 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -méthylprégna-1,4-diène-3,20-dione
 17-acétate 21-valérate de 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -méthylprégna-1,4-diène-3,20-dione
 17-acétate 21-benzoate de 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -méthylprégna-1,4-diène-3,20-dione
 17-propionate 21-butyrate de 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -méthylprégna-1,4-diène-3,20-dione
 17-propionate 21-valérate de 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -méthylprégna-1,4-diène-3,20-dione
 17-butyrate 21-acétate de 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -méthylprégna-1,4-diène-3,20-dione
 17-butyrate 21-propionate de 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -méthylprégna-1,4-diène-3,20-dione
 17,21-dibutyrate de 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -méthylprégna-1,4-diène-3,20-dione
 17-butyrate 21-valérate de 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -méthylprégna-1,4-diène-3,20-dione
 17-butyrate 21-benzoate de 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -méthylprégna-1,4-diène-3,20-dione
 17-valérate 21-propionate de 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -méthylprégna-1,4-diène-3,20-dione
 17-valérate 21-butyrate de 9 α -chloro-11 β ,17 α ,21-trihydroxy-16 α -méthylprégna-1,4-diène-3,20-dione.

3. Procédé de préparation des composés de la revendication 1, caractérisé en ce qu'on fait réagir un composé de la formule:

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(II)

dans laquelle R₁ et R₂ sont tels que définis dans la revendication 1, avec de l'acide chlorhydrique gazeux.

4. Procédé suivant la revendication 3, caractérisé en ce que l'on mélange un excès d'acide chlorhydrique gazeux avec un solvant organique ou avec de l'eau et en ce qu'on contrôle la température de réaction entre -60°C et +20°C.

5. Procédé suivant la revendication 4, caractérisé en ce qu'on contrôle la température de réaction entre -20°C et +10°C.

6. Procédé suivant l'une ou l'autre des revendications 3 et 4, caractérisé en ce que l'on isole le produit final de la réaction par mélange avec un non-solvant à une température d'environ 0°C et en ce que le pH final du mélange de réaction se situe entre 3 et 7.

7. Procédé suivant la revendication 6, caractérisé en ce que le non-solvant est constitué par de l'eau et de la glace et en ce qu'on ajuste le pH avec du carbonate ou du bicarbonate de sodium, une solution d'ammoniac ou une amine organique.

8. Composition pharmaceutique qui contient un composé de formule I, tel que défini à la revendication 1, avec un support pharmaceutique.

9. Composition pharmaceutique suivant la revendication 8, qui contient l'un quelconque des composés revendiqués à la revendication 2.